EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

The application has been amended as follows:

In the specification, at page 3, lines 23-30, please delete the existing paragraph and replace with the following, amended paragraph:

A more recent strategy has been to target the vasculature of solid tumors. Targeting the blood vessels of the tumors, rather than the tumor cells themselves, has certain advantages in that it is not likely to lead to the development of resistant tumor cells, and that the targeted cells are readily accessible. Moreover, destruction of the blood vessels leads to an amplification of the anti-tumor effect, as many tumor cells rely on a single vessel for their oxygen and nutrients (Denekamp, 1990). Effective vascular targeting strategies are described in U.S. Pat. Nos. 5,855,866 and 5,965,132 ~~5,___,___ (U.S. application Ser. No. 08/350,212, Issue Fee paid)~~, which particularly describe the targeted delivery of anti-cellular agents and toxins to tumor vasculature.

In the specification, at page 4, lines 1-13, please delete the existing paragraph and replace with the following, amended paragraph:

Another effective version of the vascular targeting approach is to target a coagulation factor to tumor vasculature (Huang et al, 1997; U.S. Pat. Nos. 5,877,289, 6,004,555, 6,093,399 ~~5,___,___ and 5,___,___ (U.S. application Ser. Nos. 08/487,427 and 08/482,369; Issue Fees paid)~~). The use of antibodies and other targeting agents to deliver coagulants to tumor vasculature has the further advantages of reduced immunogenicity and even lower risk of toxic side effects. As disclosed in U.S. Pat. No. 5,877,289, a preferred coagulation factor for use in such tumor-specific thrombogens, or "coaguligands", is a truncated version of the human coagulation-inducing protein, Tissue Factor (TF). TF is the major initiator of blood coagulation (Ruf et al., 1991; Edgington et al., 1991; Ruf and Edgington, 1994). Treatment of tumor-bearing mice with such coaguligands results in significant tumor necrosis and even complete tumor regression in many animals (Huang et al., 1997; U.S. Pat.

Nos. 5,877,289, 6,004,555, and 6,093,399 ~~5,___,___ and 5,___,___ (U.S. applications Ser. Nos. 08/487,427 and 08/482,369; Issue Fees paid)~~).

In the specification, at page 38, lines 13-22, please delete the existing paragraph and replace with the following, amended paragraph:

Tumor vasculature-targeted cytotoxic agents are described in the following patents and patent applications: U.S. Pat. Nos. 5,855,866; 5,776,427; 5,863,538; ~~and~~ 5,660,827; 6,004,554; 5,965,132 and 6,051,230; and U.S. application Ser. No. 07/846,349 ~~and U.S. applications Ser. Nos. 07/846,349; 08/295,868 (U.S. Pat. No. 5,___,___; Issue Fee paid); 08/350,212 (U.S. Pat. No. 5,___,___; Issue Fee paid); and 08/457,869 (Notice of Allowance Received)~~; each incorporated herein by reference. Tumor targeted coagulants are described in the following patents and patent applications: U.S. Pat. Nos. 5,855,866; ~~and~~ 5,877,289; 5,965,132; 6,004,555; 6,036,955; and 6,093,399; and U.S. application Ser. No. 07/846,349 ~~U.S. applications Ser. Nos. 07/846,349; 08/350,212 (Patent No. 5,___,___; Issue Fee paid); 08/482,369 (U.S. Pat. No. 5,___,___; Issue Fee paid); 08/487,427 (U.S. Pat. No. 5,___,___; Issue Fee paid); and 08/479,727 (U.S. Pat. No. 5,___,___; Issue Fee paid)~~; each incorporated herein by reference.

In the specification, at page 39, lines 4-12, please delete the existing paragraph and replace with the following, amended paragraph:

The recombinant, truncated form of tissue factor (tTF), lacking the cytosolic and transmembrane domains, is a soluble protein that has about five orders of magnitude lower coagulation inducing ability than native TF (Stone e al., 1995; Huang el al., 1997). This is because TF needs to be associated with phospholipids for the complex with Vlla to activate IXa or Xa efficiently. However, when tTF is delivered to tumor vascular endothelium by means of a targeting antibody or agent, it is brought back into proximity to a lipid surface and regains thrombogenic activity (Huang et al., 1997; U.S. Pat. Nos. 5,877,289, 6,004,555 and 6,093,399 ~~5,___,___ and 5,___,___ (U.S. application Ser. Nos. 08/487,427 and 08/482,369; Issue Fees paid)~~). A coaguligand is thus created that selectively thromboses tumor vasculature.

In the specification, at page 39, lines 14-19, please delete the existing paragraph and replace with the following, amended paragraph:

Truncated TF has several advantages that commend its use in vascular targeted coaguligands: human tTF is readily available, and the human protein will have negligible or low immunogenicity in man; human tTF is fully functional in experimental animals, including mice; and targeted tTF is highly potent because it triggers the activation of a cascade of coagulation proteins, giving a greatly amplified effect (U.S. Pat. Nos. 5,877,289, 6,004,555, and 6,093,399 ~~5,___,___ and 5,___,___ (U.S. application Ser. Nos. 08/487,427 and 08/482,369; Issue Fees paid)~~).

In the specification, at page 39, line 28 to page 40, line 4, please delete the existing paragraph and replace with the following, amended paragraph:

Adsorbed targets are another suitable group, such as VEGF, FGF, TGF.beta., HGF, PF4, PDGF, TIMP, a ligand that binds to a TIE or a tumor-associated fibronectin isoform (U.S. Pat. Nos. 5,877,289, 6,004,555, and 6,093,399 ~~5,___,___ and 5,___,___; corresponding to U.S. Ser. Nos. 08/350,212 and 08/487,427; Issue Fees paid~~; each incorporated herein by reference). Fibronectin isoforms are ligands that bind to the integrin family of receptors. Tumor-associated fibronectin isoforms are targetable components of both tumor vasculature and tumor stroma. The monoclonal antibody BC-1I (Carnemolla et al., 1989) specifically binds to tumor-associated libronectin isoforms.

In the specification, at page 40, lines 6-12, please delete the existing paragraph and replace with the following, amended paragraph:

Other targets inducible by the natural tumor environment or following intervention by man are also targetable entities, as described in U.S. Pat. Nos. 5,776,427, 5,863,538 and 6,036,955 ~~5,___,___ (U.S. Ser. No. 08/479,727, Issue Fee paid~~; each incorporated herein by reference~~)~~. When used in conjunction with prior suppression in normal tissues and tumor vascular induction, MHC Class II antigens may also be employed as targets (U.S. Pat. Nos. 5,776,427; 5,863,538; 6,044,554 and 6,036,955 each incorporated herein by reference ~~5,___,___ and 5,___,___ (U.S. Ser. Nos. 08/295,868 and 08/479,727, Issue Fees paid); each incorporated herein by reference~~).

In the specification, at page 40, lines 14-19, please delete the existing paragraph and replace with the following, amended paragraph:

One currently preferred target for clinical applications is vascular endothelial adhesion molecule-1 (VCAM-1) (U.S. Pat. Nos. 5,855,866, 5,877,289, 6,004,555 and 6,093,399 ~~5,___,___ and 5,___,___ (corresponding to U.S. Ser. Nos. 08/482,369 and 08/487,427, Issue Fees paid);~~ each incorporated herein by reference). VCAM-1 is a cell adhesion molecule that is induced by inflammatory cytokines IL-1.alpha., IL-4 (Thornhill et al., 1990) and TNF.alpha. (Munro, 1993) and whose role in vivo is to recruit leukocytes to sites of acute inflammation (Bevilacqua, 1993).

In the specification, at page 40, line 29 to page 41 line 6, please delete the existing paragraph and replace with the following, amended paragraph:

Certain of the data presented herein even further supplement those provided in U.S. Pat. No. 5,855,855, ~~and~~ 5,877,289 and 6,004,555 each incorporated herein by reference ~~5,___,___ (corresponding to U.S. Ser. No. 08/487,427, Issue Fee paid; each incorporated herein by reference)~~ and show the selective induction of thrombosis and tumor infarction resulting from administration of an anti-VCAM-1.multidot.tTF coaguligand. The results presented were generated using mice bearing L540 human Hodgkin lymphoma. When grown as a xenogratt in SCID mice, this tumor shows close similarity to the human disease with respect to expression of inflammatory cytokines (Diehl et al, 1985) and the presence of VCAM-1 and other endothelial cell activation molecules on its vasculature.

In the specification, at page 41 lines 8-17, please delete the existing paragraph and replace with the following, amended paragraph:

Using a covalently-linked anti-VCAM-1.multidot.tTF coaguligand, in which tTF was directly linked to the anti-VCAM-1 antibody, it is shown herein that the coaguligand localizes selectively to tumor vessels, induces thrombosis of those vessels, causes necrosis to develop throughout the tumor and retards tumor growth in mice bearing solid L540 Hodgkin tumors. Tumors generally needed to be at least about 0.3 cm in diameter to respond to the coaguligand, because VCAM-1 was absent from smaller tumors. Presumably,

in small tumors, the levels of cytokines secreted by tumor cells or host cells that infiltrate the tumor are too low for VCAM-1 induction. This is in accordance with the studies in U.S. Pat. Nos. 5,855,866, 5,877,289, 5,776,427, 6,004,555 and 6,036,955 ~~5,___,___, and 5,___,___ (Ser. Nos. 08/487,427 and 08/479,727, Issue Fees paid)~~, where the inventions were shown to be most useful in larger solid tumors.

In the specification, at page 41 lines 19-26, please delete the existing paragraph and replace with the following, amended paragraph:

Although VCAM-1 staining was initially observed more in the periphery of the tumor, the coaguligand evidently bound to and occluded blood transporting vessels--as it was capable of curtailing blood flow in all tumor regions. Furthermore, one of the inventors contemplates that the thrombin generation caused by the initial administration of the coaguligand likely leads to further VCAM-1 induction on central vessels (Sluiter et al., 1993), resulting in an amplified signal and evident destruction of the intratumoral region. This type of coagulant-induced expression of further targetable markers, and hence signal amplification, is also disclosed in U.S. Ser. No. 08/479,727 and U.S. Pat. No. 6,036,955 ~~08/481,904 (U.S. Pat. No. 5,___,___; Issue Fee paid)~~.

In the specification, at page 99 lines 11-17, please delete the existing paragraph and replace with the following, amended paragraph:

The following patents and patent applications are specifically incorporated herein by reference for the purposes of even further supplementing the present teachings regarding the preparation and use of functional, antigen-binding regions of antibodies, including scFv, Fv, Fab', Fab and F(ab').sub.2 fragments of the anti-aminophospholipid antibodies: U.S. Pat. Nos. 5,855,866, ~~and~~ 5,877,289, 5,965,132; 6,004,555; and 6,093,399 ~~; and U.S. application Ser. Nos. 08/350,212 (U.S. Pat. No. 5,___,___ Issue Fee paid); 08/482,369 (U.S. Pat. No. 5,___,___; Issue Fee paid); and 08/487,427 (U.S. Pat. No. 5,___,___; Issue Fee paid)~~.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRANDON J. FETTEROLF whose telephone number is

(571)272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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